TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED OFFICE (DO/US)

PCT/SE00/01310	20 JUNE 2000	22 JUNE 1999
International Application Number	International Filing Date	Priority Date(s) Claimed

NEW FORMULATION
Title of Invention

LUNDBERG, Per Johan and SJÖBLOM, Brita

Applicant(s) for DO/US

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Date of Deposit SEPTEMBER 22, 2000.
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To the United States Designated Office (DO/US):

I. Accompanying this transmittal letter are certain items which are required under 35 U.S.C. 371 in order that United States National processing of the above identified International application may commence:

(X) at the expiration of the applicable time limit under PCT Articles 22 and 39(1) according to the provisions of 35 U.S.C. 371(b).

( ) as soon as possible upon receipt of this express request under 35 U.S.C. 371(f).

1. The U.S. National fee [35 U.S.C. 371(c)(1)]

a. ( ) was previously transmitted by applicant on (date)____.

b. (**X**) is submitted herewith as follows:

FOR	NO. FILED	NO. EXTRA	SMALL ENTITY RATE	FEE	or	OTHER THAN SMALL ENTITY RATE	FEE
Basic Fee	(USPTO NOT ISA OR IPEA)		////	$485	or	/////	**$970**
Total Claims	-20 =	--	x 9 =		or	x18 =	**$**
Ind. Claims	**1 - 3**	--	x 39 =		or	x78 =	**$**
(**X**) Multiple Dependent Claim Presented			+130 =		or	+260 =	**$260**
	TOTAL NATIONAL FEE		$____		or		**$1230**

i. (**X**) A check in the amount of **$1230** is enclosed.

ii. ( ) Please charge the filing fee, multiple dependent claim fee (if applicable), excess independent claims fee (if applicable), and excess total claims fee (if applicable) **to Deposit Account No. 23-1703**.

iii. (**X**) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to **Deposit Account No. 23-1703**. A duplicate copy of this sheet is enclosed.

(iv) ( ) The filing fee is not enclosed.

2. A copy of the International application as filed [35 U.S.C. 371(c)(2)]:

a. (**X**) is transmitted herewith.

b. ( ) is not required as the application was filed with the United States Receiving Office.

c. ( ) has been transmitted

i. ( ) by the International Bureau. Date of mailing of the application (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed.

ii. ( ) by applicant on (date) _____.

3. A translation of the International application into the English language [35 U.S.C. 371(c)(2)]:

a. ( ) is transmitted herewith.

b. (X) is not required as the application was filed in English.

c. ( ) was previously transmitted by applicant on (date)_____.

4. Amendments to the claims of the International application under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) are transmitted herewith.

b. ( ) have been transmitted

i. ( ) by the International Bureau. Date of mailing of the amendments (from form PCT/IB/308): _____.

ii. ( ) by applicant on (date) _____.

c. (X) have not been transmitted as

i. ( ) no notification has been received that the International Searching Authority has received the Search Copy.

ii. ( ) the Search Copy was received by the International Searching Authority but the Search Report has not yet issued. Date of receipt of Search Copy (from form PCT/ISA/202): _____.

iii. ( ) applicant chose not to make amendments under PCT Article 19. Date of mailing of Search Report (from form PCT/ISA/210):

iv. (X) the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

5. A Translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)]:

a. ( ) is transmitted herewith.

b. ( ) is not required as the amendments were made in the English language.

c. (X) has not been transmitted for reasons indicated at point I.4.b. or c. above.

6. An executed declaration for patent application of the inventor [35 U.S.C. 371(c)(4)] complying with 35 U.S.C. 115:

a. ( ) was previously submitted by applicant on (date) _____

b. (X) is submitted herewith; and such oath or declaration

i. (X) is attached to the application.

ii. (X) identifies the application and any amendments under PCT Article 19 which were transmitted as stated in points 1.2.b. or c. and 1.4. and states that they were reviewed by the inventor as required by 37 CFR 1.70.

c. ( ) will be submitted subsequently.

II. Concerning other documents:

1. An International Search Report or Declaration under PCT Article 17(2)(a):

a. ( ) has been transmitted by the International Bureau. Date of mailing (from form PCT/IB/308): _____ A copy of form PCT/IB/308 is enclosed

b. ( ) is not required as the application was searched by the United States International Searching Authority.

c. ( ) A copy of the International Search Report is transmitted herewith.

d. ( ) has been submitted by applicant on (date) _____.

2. A Statement of prior art under 37 CFR 1.97 and 1.98:

a. ( ) is transmitted herewith including copies of the references cited on the attached form PTO-1449. Also enclosed is a copy of the International-Type Search Report (PCT/ISA/201/SE), issued in the Swedish priority application.

b. ( ) will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).

c. ( ) was previously submitted by applicant on _____, in application serial no. _____.

3. (X) An executed Assignment is transmitted herewith for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

a. ( ) Please charge the $40.00 assignment recordation fee to Deposit Account No. 23-1703.

b. (X) Enclosed is a check in the amount of **$40**.

4. **Other document(s) or information included:**
- Copy of PCT/RO/101 - The PCT Request Form;
- One sheet of drawings; and
- Return postcard.

Respectfully submitted,

22 September 2000
DATE

John M. Genova
Reg. No. 32,224
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enclosures

Barbara Caldwell

1103326-0636

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	: Lundberg et al.
Serial No.	: 09/646,852
Filed	: September 22, 2000
For	: NEW FORMULATION
Examiner	: To be assigned
Group Art Unit	: To be assigned

CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on December 18, 2001 at the facsimile number 703-305-3230.

Andrew Fessak 48,528
Agent Name PTO Reg. No.

Andrew Fessak 12/18/01
Signature Date of Signature

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

FACSIMILE NO: **703-305-3230**
DATE: **December 18, 2001**
PAGES: **11 pages**

PRELIMINARY AMENDMENT

Sir:

Preliminary to examination on the merits, please amend the referenced application as follows:

IN THE CLAIMS:

Replace claims 1, 3-20, and 23-24 as filed with amended claims 1, 3-20, and 23-24. Cancel claims 2, 21, and 22. Add new claims 25 and 26.

1. (Amended) An oral pharmaceutical dosage form comprising a core material coated with a semipermeable membrane, wherein:
the core material comprises an active ingredient selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients;
the membrane comprises a water-insoluble polymer and a modifying agent and is able to disrupt; and the dosage form is not enteric coated.

3. (Amended) The dosage form according to claim 1, wherein the active ingredient is omeprazole.

4. (Amended) The dosage form according to claim 1, wherein the active ingredient is a magnesium salt of omeprazole having a crystallinity of more than 70% as determined by X-ray powder diffraction.

5.(Amended) The dosage form according to claim 1, wherein the active ingredient is a magnesium salt of *S*-omeprazole.

6. (Amended) The dosage form according to claim 1, wherein the core material comprises a sugar sphere layered with a suspension or solution of the active ingredient, one or more alkaline additives, one or more swelling agents and optionally pharmaceutically acceptable excipients.

7. (Amended) The dosage form according to claim 1, wherein the dosage form comprises individual pellets of the core material coated with the semipermeable membrane.

8. (Amended) The dosage form according to claim 1, wherein the core material further comprises an osmotic agent.

9. (Amended) The dosage form according to claim 1, wherein the alkaline additive gives a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode.

10. (Amended) The dosage form according to claim 9, wherein the alkaline additive is selected from the group consisting of disodium hydrogen phosphate, trisodium phosphate, arginine and talc.

11. (Amended) The dosage form according to claim 1, wherein the alkaline additive is present in an amount of approximately 5 to 35% by weight of the core material excluding the weight of an optional sugar sphere.

12. (Amended) The dosage form according to claim 1, wherein the alkaline additive is present in an amount of 15 to 35% by weight of the core material excluding the weight of an optional sugar sphere.

13. (Amended) The dosage form according to claim 1, wherein the swelling agent is selected from the group consisting of crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC).

14. (Amended) The dosage form according to claim 1, wherein the swelling agent is present in an amount of approximately 20 to 60% by weight of the core material excluding the weight of an optional sugar sphere.

15. (Amended) The dosage form according to claim 1, wherein the swelling agent is present in an amount of 30 to 50% by weight of the core material excluding the weight of an optional sugar sphere.

16. (Amended) The dosage form according to claim 1, wherein the modifying agent is talc or fumed silica.

17. (Amended) The dosage form according to claim 1, wherein the water insoluble polymer is selected from the group consisting of ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B.

18. (Amended) The dosage form according to claim 1, wherein the water insoluble polymer is present in an amount of approximately 3-30% by weight of the core material.

19. (Amended) The dosage form according to claim 1, wherein the modifying agent and water insoluble polymer are in a ratio of between 90:10 and 50:50.

20. (Amended) A process for the manufacture of a dosage form as defined in claim 1, comprising forming a core material comprising an active ingredient selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable

excipients, and coating the core material with a semipermeable membrane, wherein the dosage form has no enteric coating.

23. (Amended) A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form according to any one of claims 1 or 3-19.

24. (Amended) A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form according to any one of claims 1 or 3-19.

25. (New) An oral dosage form according to any one of claims 1 or 3-19 filled in a capsule.

26. (New) An oral dosage form according to any one of claims 1 or 3-19 compressed into a multiple unit tableted dosage form, optionally comprising tablet excipients.

REMARKS

Amendments

Claims 1, 3-20, and 23-24 have been amended to place the claims in accordance with U.S. patent practice, and to reflect amendments entered in the international stage of application PCT/SE00/01310, of which the instant application is the U.S. national stage. Claim 1 has been amended to incorporate embodiments of the inventions deleted from original claims 2, 16, and 19. Thus, amended claim 16 is now directed solely to exemplary embodiments of the modifying agent, and amended claim 19 now recites solely the ratio between the modifying agent and the water-insoluble polymer. Claims 2, 21, and 22 have been canceled.

New claim 25 is directed to an embodiment of the invention wherein the dosage form is filled in a capsule. Support for claim 23 is found on page 5, lines 12-13, and page 9, lines 3-4. New claim 26 is directed to an embodiment of the invention wherein the dosage form is compressed into a tableted dosage form. Support for claim 26 is found on page 9, lines 3-10.

No new matter is introduced by any of the amendments herein.

CONCLUSION

Upon entry of this Preliminary Amendment, claims 1, 3-20, and 23-26 are pending Applicants respectfully submit that claims 1, 3-20, and 23-26 are directed to patentable subject matter. Accordingly, Applicants request allowance of the claims.

Authorization is hereby given to charge any fee in connection with this communication to Deposit Account No. 23-1703.

Dated: Dec. 18, 2001

Respectfully submitted,

Andrew Fessak

Andrew Fessak
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Agent for Applicants

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Claims 1, 3-20, and 23-24- Version with markings to show changes made

1. (Amended) An oral pharmaceutical dosage form comprising a core material coated with a semipermeable membrane, wherein:

the core material comprises an active ingredient selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, [in admixture with] one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients; [,]

the membrane comprises a water-insoluble polymer and a modifying agent and is able to disrupt; and the dosage form is not enteric coated.

3. The [A] dosage form according to claim 1, wherein the active ingredient is omeprazole.

4. The [A] dosage form according to claim 1, wherein the active ingredient is a magnesium salt of omeprazole having a crystallinity of more than 70% as determined by X-ray powder diffraction.

5. The [A] dosage form according to claim 1, wherein the active ingredient is a magnesium salt of *S*-omeprazole.

6. The [A] dosage form according to claim 1, wherein the core material comprises a sugar sphere layered with a suspension or solution of the active ingredient, one or more alkaline additives, one or more swelling agents and optionally pharmaceutically acceptable excipients.

7. The [A] dosage form according to claim 1, wherein the dosage form comprises individual pellets of the core material coated with the semipermeable membrane.

8. The [A] dosage form according to claim 1, wherein the core material [comprises a] further comprises [component in the form of] an osmotic agent.

9. The [A] dosage form according to claim 1, wherein the alkaline additive [is an agent selected from the group of compounds that] gives a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode.

10. The [A] dosage form according to claim 9, wherein the alkaline additive is [an agent] selected from the group consisting of disodium hydrogen phosphate, trisodium phosphate, arginine and talc.

11. The [A] dosage form according to claim 1, wherein the alkaline additive is present in an amount of approximately 5 to 35% by weight of the core material excluding the weight of an optional sugar sphere.

12. The [A] dosage form according to claim 1, wherein the alkaline additive is present in an amount of 15 to 35% by weight of the core material excluding the weight of an optional sugar sphere.

13. The [A] dosage form according to claim 1, wherein the swelling agent is selected from the group consisting of crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC).

14. The [A] dosage form according to claim 1, wherein the swelling agent is present in an amount of approximately 20 to 60% by weight of the core material excluding the weight of an optional sugar sphere.

15. The [A] dosage form according to claim 1, wherein the swelling agent is present in an amount of 30 to 50% by weight of the core material excluding the weight of an optional sugar sphere.

16. The [A] dosage form according to claim 1, wherein the [semipermeable membrane comprises a water insoluble polymer and a] modifying agent is [such as] talc or fumed silica

17. The [A] dosage form according to claim 1, wherein the water insoluble polymer is selected from the group consisting of ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B.

18. The [A] dosage form according to claim 1, wherein the water insoluble polymer is present in an amount of approximately 3-30% by weight of the core material.

19. The [A] dosage form according to claim 1, wherein the [semipermeable membrane comprises a] modifying agent and [a] water insoluble polymer are in a ratio of between 90:10 and 50:50.

20. A process for the manufacture of a dosage form as defined in claim 1, comprising forming [wherein] a core material comprising [is formed comprises] an active ingredient selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, [in admixture with] one or more alkaline additives, one or more swelling agents, and

optionally pharmaceutically acceptable excipients, and coating the core material [is coated] with a semipermeable membrane, wherein the dosage form [and] has no enteric coating.

23. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form according to any one of claims 1 or 3-19 [as defined in any of claims 1 – 19].

24. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form according to any one of claims 1 or 3-19 [as defined in any of claims 1 – 19].

25 (New) An oral dosage form according to any one of claims 1 or 3-19 filled in a capsule.

26. (New) An oral dosage form according to any one of claims 1 or 3-19 compressed into a multiple unit tableted dosage form, optionally comprising tablet excipients.

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*** RX REPORT ***
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ST. TIME	12/18 15:35
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PGS.	11
RESULT	OK

Applicant: **AstraZeneca AB**
S-151 85 Södertälje
Sweden

Title: **NEW FORMULATION**

Reference: H 2200-1 WO

Inventors: Lundberg, Per Johan
Sjöblom, Brita

NEW FORMULATION

Field of the invention

The present invention relates to new oral pharmaceutical dosage forms comprising as active ingredient omeprazole, an alkaline salt of omeprazole, *S*-omeprazole or an alkaline salt of *S*-omeprazole. The dosage form comprises a core material of the active ingredient, one or more alkaline additives, and one or more swelling agents, wherein the core material is covered with a semipermeable membrane and without an enteric coating. Furthermore, the invention refers to the manufacture of such dosage forms and their use in medicine.

Background of the invention and prior art.

The acid labile H^+, K^+-ATPase inhibitor known under the generic name omeprazole is disclosed in EP-0005129. Certain salts of omeprazole are described in EP-124495, a magnesium salt of omeprazole is described in WO 95/01977, and the single enantiomers of omeprazole and certain salts thereof are described in WO 94/27988.

Omeprazole is useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrome. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease (GORD). Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis

as well as in the treatment of *Helicobacter* infections and diseases related to these where therapeutic control of gastric acid secretion is fundamental in the treatment.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light. With respect to the stability properties of omeprazole, it is established that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, US 4,786,505 describes such enteric coated formulations. These formulations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and further with an enteric coating layer. There are numerous published patent applications from different companies describing enteric coated formulations comprising omeprazole or other proton pump inhibitor compounds.

WO 96/01623 describes tableted dosage forms of omeprazole, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces.

There are different technologies and pharmaceutical formulations described in the prior art which provide a delayed release of an administered drug. Such formulations are for instance based on osmotic differences, slow-eroding/dissolving layers, diffusion through a membrane, time controlled explosion systems or any combinations thereof. In the following some of these principles are exemplified. For instance, US 4 871 549 describes a time controlled explosion system. Conte et al (Drug Development and Industrial

Pharmacy, 1989, vol. 15, pp. 2583 –96) describes a three-layer tablet giving a double pulsed system suitable for ibuprofen. US 5 567 441 describes a dosage form for diltiazem comprising a mixture of one fraction of slow release pellets and another fraction of delayed pulse release membrane coated pellets. WO97/02020 describes a dosage form of pantoprazole in combination with antibacterial substances wherein one part of the pantoprazole dose is in slow release form with a continuously release during time. US 5 178 867 describes a dosage form with an exit port or hole that connects the interior of the dosage form with the exterior.

Summary of the invention

The present invention provides - in contrast to earlier presented oral dosage forms for proton pump inhibitor compounds - a dosage form without an enteric coating layer.

The dosage form according to the present invention comprises a core material coated with a semipermeable membrane. The core material contains an active ingredient selected from omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof, one or more alkaline additives, and one or more swelling agents. The semipermeable membrane is able to disrupt or may change its permeability after a pre-determinated time. One or more swelling agents are placed in the core material to effectuate a disruption or an increased permeability of the semipermeable membrane after such a suitable time. Optionally pharmaceutically acceptable excipients such as an osmotic agent may also be included in the core material.

Surprisingly, the formulation according to the present invention is prepared without an enteric coating, which previously have been almost an axiom for dosage forms containing omeprazole or any other proton pump inhibitor compounds. The present invention also provides the possibility to avoid the separating layer needed under an enteric coating layer to separate omeprazole from the enteric coating polymer. Omeprazole should preferably not be in contact with the enteric coating due to discoloration and degradation of

omeprazole. Thus, the present invention provides a simplified process than previous manufacture processes requesting double coating layers on the core material. See for instance, EP 247 983.

According to a further aspect of the present invention, the dosage form may preferably be in the form of a multiple unit pellet system. The prepared core material, in the form of small pellets coated with a semipermeable membrane and without an enteric coating may be filled into a capsule or compressed into a multiple unit tablet.

The core material comprises an alkalizing agent, that is sufficiently alkaline and is present in a sufficiently high amount. The core material also comprises a swelling agent that upon contact with moisture starts to swell. When the coated pellets pass the stomach small amounts of gastric fluid will be absorbed through the semipermeable membrane. The alkalizing agent in the core material will neutralize the absorbed acidic fluid and protect the active ingredient against degradation. At the same time the swelling agent, will be exposed to the penetrating fluid or moisture, and it will start to expand. After a pre-determined time interval this expansion leads to disruption of the superimposed semipermeable membrane by the built-up pressure or to a swelling that will increase the permeability of the membrane. The time interval is to be determined so that the pellets have had time to pass the stomach at that very moment, and have reached the small intestines. The entire dose of the active ingredient will then start to be released into the small intestine where absorption can occur.

Detailed description of the drawings

Figures 1 – 4 illustrate principles for construction of dosage forms according to the present invention. The invention comprises a core material layered with a semipermeable membrane. The core material can be prepared according to at least four different principles as shown in the Figures. The drawings are not intended to illustrate the size or relative sizes of the dosage form or its different parts.

Detailed description of the invention

The present invention provides a core material in the form of pellets or small tablets coated with a semipermeable membrane. The composition of the core material protect the active ingredient against the gastric fluid, that permeates through the semi permeable coating during the pellet's passage through the stomach. Such pellet formulations are generally emptied from the stomach within 2-4 hours. When the pellets have left the stomach, the semipermeable membrane covering the individual pellets disrupts and/or starts to release the active ingredient in the small intestine.

The pellets coated with the semipermeable membrane may be filled into capsules prepared from gelatine or hydroxypropyl methylcellulose (HPMC), be filled into sachets or be mixed with tablet excipients and compressed to a fast disintegrating tablet or to an effervescent tablet.

Core material

The core material may be produced with starter seeds, for instance sugar spheres like Non-pareils™, by layering the active ingredient on the seeds by conventional technique or by the use of a centrifugal granulator/ roto granulator. Alternatively, the core material has a homogenous distribution of the active agent and excipients, and is prepared e.g. by extrusion and spheronization, or by compression. Other conventional techniques known in the art are also suitable in preparing the core material.

The core material is in the form of pellets, spheroids or small tablets. The size of the formulated core materials is approximately between 0.1 and 4 mm, and preferably the core material has a diameter of 0.2 to 2.5 mm.

The core material comprises the active ingredient, an alkalizing agent, a swelling agent and optionally binders, osmotic agents and other pharmaceutically acceptable excipients.

The active ingredient is selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof. Suitable alkaline salts are for instance the Mg^{2+}, Ca^{2+}, Na^{+}, K^{+} salts, preferably the Mg^{2+} salts in a highly crystalline form. A preferred magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffration is described in WO95/01977, hereby incorporated by references.

Before the seeds are layered, the active ingredient may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active ingredient in the final mixture.

Such further components can be binders, surfactants, fillers or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example cellulose derivatives such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, and others such as polyvinyl pyrrolidone, gelatine, sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulphate.

An alkalizing agent is incorporated in the core material together with the active ingredient and/or the swelling agent, preferably together with the active ingredient. The alkalizing agent is present in an amount of approximately 5 to 35 % w/w in the core material, preferably 10 to 35 % w/w, or most preferably 15 to 35 % by weight calculated on the weight of the core material excluding the weight of the optional starter seed.

The alkalizing agent is selected from compounds like disodium hydrogen phosphate, trisodium phosphate, arginine or talc etc, provided that they give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode. At least one alkalizing agent has to be incorporated in the core material, but also any combinations of alkalizing agents can be used.

The swelling agent is selected among pharmaceutically acceptable disintegrants, preferably among crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate or low-substituted hydroxypropyl cellulose (L-HPC), alone or in any combinations. The amount of swelling agent is pre-determined to effectuate the start of dissolution of the core material at a proper time. Preferably, the core material comprises approximately 20 to 60 % by weight of the swelling agent calculated on the weight of the core material excluding any optional starting seed. More preferably a concentration of 25 to 55 % by weight, or especially 30 to 50 % by weight of the swelling agent calculated in the same manner.

Alternatively, the swelling agent or a portion of the swelling agent may optionally be prepared and incorporated in a separate layer. Such a separate layer will cover the core material and also comprise binders and optionally an alkalizing agent and/or pharmacetically acceptable excipients.

Optionally, an osmotic agent is incorporated in the core material. Such an osmotic agent is watersoluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulphate, sodium chloride, lithium chloride, potassium chloride, potassium sulphate, sodium carbonate, lithium sulphate, calcium bicarbonate, sodium sulphate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

Alternatively, the active ingredient, optionally mixed with any of the components defined above, can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing different process equipments.

For extrusion/spheronization processes incorporation of a microcrystalline cellulose and a low-substituted hydroxypropylcellulose in the core material is preferred.

Semipermeable membrane.

The membrane comprises a water insoluble polymer and a modifying additive and optionally pharmaceutically acceptable excipients like fillers, colorants etc. The excipients should be insoluble or hardly soluble in acidic solutions, or present in such amounts that they do not influence the solubility properties of the membrane.

Preferably, water insoluble polymer may be selected among semipermeable water insoluble polymers like ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B (Eudragit RL, Eudragit RS) etc.

The modifying agent in the semipermeable membrane may be a talc or fumed silica (e.g. Aerosil or Cab-O-Sil.). Preferably an alkaline reacting modifying agent such as talc is used.

Preferred composition of the semipermeable membrane comprises an amount of modifying agent to water insoluble polymer on a weight to weight ratio of from 90:10 up to 50:50. Preferably the amount of modifying agent to water insoluble polymer on a weight to weight ratio is from 80:20 up to 60:40 in the membrane.

The core material will be layered with a sufficient amount of the semipermeable membrane composition to cover the core material. Preferably, the amount of semipermeable membrane applied is approximately 3-30% by weight of the weight of the core material. The amount of semipermeable membrane for a desired dosage form is adjusted to obtain a desired lagtime and an adequate dissolution.

Final dosage form

The prepared core material coated with the semipermeable membrane is filled into a capsule (gelatine or HPMC capsule), or optionally mixed with tablet excipients and compressed into a multiple unit tableted dosage form. In the expression "tablet excipients" is also effervescent tablet excipients included when referring to multiple unit tablets. Prepared tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and/or to further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The claimed dosage forms are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of severe conditions higher doses than average may be used.

Preferably, a dosage form comprising for instance 1 - 100 mg of omeprazole or S-omeprazole will be administered once a day. Suitable doses comprise preferably 10 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids.

Examples

The following examples describe the invention more in detail without restricting the scope of the invention.

Example 1

Core materials in the form of pellets made by extrusion and spheronization.

The following compositions were used to prepare core materials;

	Pellets A		Pellets B		Pellets C	
Compound	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets
Omeprazole	40.0		40.0		40.0	
Low-substituted Hydroxypropyl cellulose	82.0	20.6	-	-	84.0	21.0
Polyvinyl pyrrolidone crosslinked micronized	-	-	84.0	21.0	-	-
Microcrystalline cellulose PH 101	58.0		60.2		78.4	
Mannitol powder	136.0		115.0		136.5	
Sodium chloride (<0.20 mm)	60.0		20.0		40.3	
Trisodium phosphate*	20.0	4.8	-	-	-	-
Disodium hydrogen phosphate*	-	-	-	-	20.0	5.0
Arginine	-	-	80.0	20.0	-	-
Sodium lauryl sulphate	2.0		0.8		0.8	
Water purified	170	-	151	-	199	-
Total weight of dry subst.	418		400		400	

* In this example the amounts for all phosphates are indicated as free of crystal water.

The powders were mixed and then wetted with the granulating solution. When needed extra water was added afterwards, until total amount added water corresponded to the value given in the table above. The wet mass was subjected for extrusion through a screen having 1.0 mm in diameter apertures. The strings obtained were shaped to pellets in a

spheronizer operated at 350 rpm. The pellets were dried in a fluid bed apparatus with inlet air temperature set to 50 degrees Celsius.

Granulating liquid used for composition A was 2.72 g of the trisodium phosphate and all the sodium lauryl sulphate dissolved in 50 grams of the water.

Granulating liquid used for composition B was 10.0 g of the arginine and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Granulating liquid used for composition C was 8.06 g of the disodium hydrogen phosphate and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Remark: Only parts of composition B were possible to get through the extruder, however material for further experimentation was obtained.

Example 2

Core material in the form of pellets prepared by layering technique.

A drug containing suspension was made according to the composition below;

Compound	Amount
Omeprazole	219 g
HPMC, 6 cps	39.8 g
Disodiumhydrogen phosphate	42.9 g
Polysorbate 80	4.8 g
Purified water	919 g

First the polysorbate 80 was dissolved in the water. Then the phosphate was dissolved during stirring. Then the HPMC was dissolved whereafter the drug was suspended in the obtained solution. The suspension was sprayed onto 150 g of sugar spheres (Non-pareil) in

a fluidized bed. The weight of the obtained product was 355 g and the omeprazole content was 456 mg/g.

A suspension containing swellable substance was prepared according to the following composition;

		%
Cross-linked polyvinyl pyrrolidone micronized (Kollidon CL-M)	187.8 g	41*
Hydroxypropylcellulose L (HPC-L from Nisso)	46.9 g	
Talc	140.8 g	
EtOH (99.5%)	1500 g	

* % w/w of core material not including starter seed.

HPC-L was dissolved in ethanol during stirring, then the talc and swelling agent Kollidon CL-M was added. The suspension was sprayed onto 130 g of the drug-layered spheres as prepared above in a Wurster equipped fluidized bed until the omeprazole content of the obtained core material was 130 mg/g. The weight of the obtained product was 455 g.

Example 3

Membrane coated pellets.

The core material from Example 2 was coated in a fluid bed apparatus with an ethyl cellulose solution having talc suspended therein. The composition of the suspension used was:

Substance	Amount	% of dry membrane
Ethyl cellulose N-10	13.5 parts	30%
Ethanol (99.5%)	1455 parts	-
Talc	31.5 parts	70%
Total	1500 parts	100%

80 grams of core material from example 2 was coated with this suspension until the omeprazole content was 107 mg/g.

Example 4

Test of the prepared membrane coated pellets.

The prepared membrane coated core material was tested for gastric acid resistance and dissolution as described below.

Test for gastric acid resistance

The pellets were tested for gastric acid resistance by immersing them in 0.1 M HCl for 2 hrs and the determining the remaining drug fraction. The fluid phase (the HCl) had an addition of 0.1 g/liter of sodium lauryl sulphate as wetting agent. The remaining drug fraction was 96%.

Test for dissolution

Dissolution of active substance was tested accordingly, first pellets were immersed in the test-fluid described above for 2 hrs, then buffer components (phosphate salts) were added to change the pH to 6.8.

Samples of the dissolution medium were withdrawn and analyzed with HPLC at the given time intervals. Results;

Time , Hrs (after 2hrs of pre-exposure in acid medium)	% Dissolved
0.5	3
1	18
2	60
3	73

Amended Claims

1. An oral dosage form comprising a core material coated with a semipermeable membrane comprising a water-insoluble polymer and a modifying agent, said semipermeable membrane being able to disrupt, and wherein the core material comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkalizing agents, one or more swelling agents, and optionally pharmaceutically acceptable excipients, and which dosage form is not enteric coated.

2. A dosage form according to claim 1 wherein the active ingredient is omeprazole.

3. A dosage form according to claim 1 wherein the active ingredient is a magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffraction.

4. A dosage form according to claim 1 wherein the active ingredient is magnesium salt of *S*-omeprazole.

5. A dosage form according to any one of claims 1-4, wherein the core material comprises a sugar sphere layered with a suspension or solution of the active ingredient, one or more alkalizing agents, one or more swelling agents and optionally pharmaceutically acceptable excipients.

6. A dosage form according to any one of claims 1-5, wherein the dosage form comprises individual pellets of the core material coated with the semipermeable membrane.

7. A dosage form according to any one of claims 1-6, wherein the core material comprises a further component in the form of an osmotic agent.

8. A dosage form according to any one of claims 1-7, wherein the alkalizing agent is an agent selected from the group of compounds that give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode.

9. A dosage form according to any one of claims 1-8, wherein the alkalizing agent is an agent selected from the group of disodium hydrogen phoshate, trisodium phosphate, arginine and talc.

10. A dosage form according to any one of claims 1-9, wherein the alkalizing agent is present in an amount of approximately 5 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

11. A dosage form according to claim 10 wherein the alkalizing agent is present in an amount of 15 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

12. A dosage form according to any one of claims 1-11, wherein the swelling agent is selected from the group of crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC).

13. A dosage form according to any one of claims 1-12, wherein the swelling agent is present in an amount of approximately 20 to 60 % by weight of the core material excluding the weight of an optional sugar sphere.

14. A dosage form according to claim 13 wherein the swelling agent is present in an amount of 30 to 50 % by weight of the core material excluding the weight of an optional sugar sphere.

15. A dosage form according to any one of claims 1-14, wherein the modifying agent is talc or fumed silica.

16. A dosage form according to any one of claims 1-15, wherein the water insoluble polymer is selected from the group of ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B.

17. A dosage form according to any one of claims 1-16, wherein the water insoluble polymer is present in an amount of approximately 3-30% by weight of the core material.

18. A dosage form according to any one of claims 1-17, wherein the semipermeable membrane comprises a modifying agent and a water insoluble polymer in a ratio of between 90:10 and 50:50.

19. A process for the manufacture of a dosage form as defined in claim 1, wherein a core material comprising an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients is formed, the core material is coated with a semipermeable membrane being able to disrupt and which dosage form has no enteric coating.

20. Use of an oral pharmaceutical dosage form as defined in any one of claims 1 - 18 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

21. Use of an oral pharmaceutical dosage form as defined in any one of claims 1 - 18 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

22. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 – 18.

23. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 – 18.

24. An oral dosage form according to any one of claims 1-18 filled into a capsule.

25. An oral dosage form according to any one of claims 1-18 optionally mixed with tablet excipients, said dosage form being compressed into a multiple unit tableted dosage form.

Fig. 1

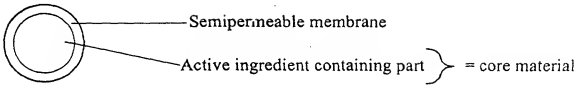


Fig. 2

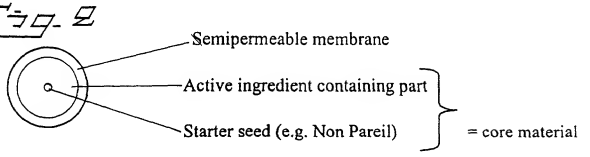


Fig. 3

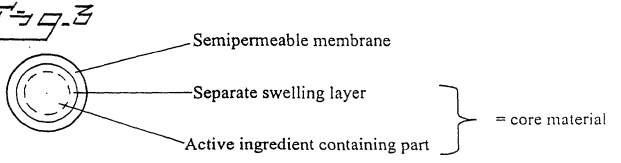
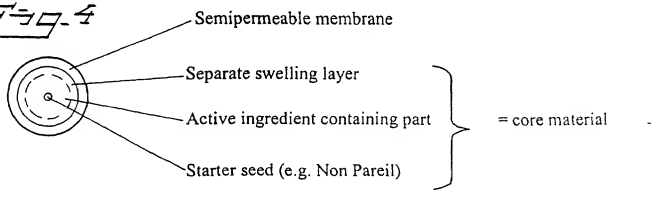


Fig. 4



Docket Number (Optional) H 2200-1P US

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled NEW FORMULATION the specification of which is attached hereto unless the following box is checked:

☒ was filed on 20 June 2000 as United States Application Number or PCT International Application Number PCT/SE00/01310 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56

☐ I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
9902386-3	Sweden	22 June 1999	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country	(Day(Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status -- patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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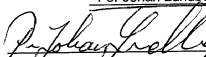
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believe to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor
(given name, family name) Per Johan Lundberg

First inventor's signature  Date: 23 Aug. 2000

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20

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Additional inventors are being named on separately numbered sheets attached hereto.